REMARKS

Status of the Claims

Claims 1 and 11-21 are pending. Claims 1, 11, 13, and 14 have been amended herein. Support for the claim amendments can be found throughout the specification, including the claims. Therefore, no new matter has been added.

Applicant respectfully requests the Examiner to reconsider and withdraw the outstanding rejections in view of the foregoing amendments and the following remarks.

Rejection under 35 U.S.C. § 101

Claim 14 is rejected under 35 U.S.C. § 101 because the claim purportedly recites a use without setting forth any steps involved in the process. Claim 14 is amended to recite the method of claim 12, wherein the administration is via the parenteral route, as proper under U.S. practice. Applicants submit that this rejection is obviated.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 12-21 are rejected under 35 U.S.C. § 112, second paragraph as purportedly indefinite for the recitation of "atypical" symptoms of gastroesophageal reflux. Applicants submit that the specification provides guidance as to atypical symptoms. For example, at page 8 of the application, at lines 1-5, atypical symptoms are listed, including asthma and dyspnoea attacks of an asthmatic type, pharyngitis, dysphonia, pseudo-angina, paroxysmal cough, and nocturnal cough. Table 3 on page 10 also lists examples of atypical symptoms. Accordingly, Applicants request that this rejection be withdrawn.

Double Patenting Rejections

Claims 1 and 11-16 are provisional rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-7 and 9 of co-pending application No. 10/561,844. Applicants will defer acting on this rejection until allowable subject matter is determined.

Claims 1 and 11-21 are provisional rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6, 14-22 of copending

application No. 11/344,212. Applicants will defer acting on this rejection until allowable subject matter is determined.

Claims 1 and 11-21 are provisional rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 9-18 of copending application No. 10/532,114. Applicants will defer acting on this rejection until allowable subject matter is determined.

Claims 1 and 11-21 are provisional rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-10 and 14-25 of U.S. Patent No. 7,034,038. Applicants will consider filing a Terminal Disclaimer as appropriate once allowable subject matter is determined in the present application.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 12-21 are rejected under 35 U.S.C. § 112, first paragraph as purportedly lacking enablement. Specifically, while the specification provides enablement for the evolution of atypical symptoms associated with gastroesophageal reflux disease, the specification purportedly does not provide enablement for the treatment of these symptoms. Applicants respectfully traverse.

As stated in *Ex parte Forman* (230 USPQ 546 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

As, the Office is aware, "[a] patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). Thus, not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be. *Staehelin v. Secher*, 24 U.S.P.Q.2d 1513, 1516 (Bd. Pat. App. & Int. 1992). Applicants submit that the specification, combined with what is known in the art, provides adequate description of how to use tenatoprazole for the treatment of nocturnal gastroesophageal reflux and Barrett's oesophagus.

First, the claims are amended herein to recite the treatment of nocturnal gastroesophageal reflux and Barrett's oesophagus. Applicants submit that a nexus between

tenatoprazole and the treatment of gastroesophageal reflux and Barrett's oesophagus does exist, and would be apparent to the skilled artisan at the time the application was filed.

Tentoprazole is known in the art as a proton pump inhibitor (PPI). Applicants submit that the amount of direction or guidance presented and the nature of the invention are such that undue experimentation would not be required to practice the claimed methods of treatment. The state of the art is such that the relationship between proton pump receptors (and the inhibition of proton pumps by PPIs) and diseases and conditions caused/related to hypersecretion of acids was well known at the time of filing. As set forth above, *Goodman & Gilman's The Pharmacological Basis of Therapeutics* and *Harrison's Principles of Internal Medicine* describe the functionality of PPIs, as well as acid-related conditions and their symptoms, which may be readily treated and relieved by PPIs. Thus, the state of the prior art and relative skill of those in the relevant art were such that undue experimentation would not be required to practice the present methods.

With regard to the scope of the presently amended claims, the breadth of the claims is commensurate with gastroesophageal reflux and Barrett's oesophagus, all relating to gastric acid. As noted in the specification at pages 1-2, gastroesophageal reflux is thought to due to a disorder of esophageal motility, allowing reflux of stomach contents, including acid, into the esophagus. Barrett's esophagus is a condition in which the esophagus, the muscular tube that carries food and saliva from the mouth to the stomach, changes so that some of the lining is replaced by a type of tissue similar to that normally found in the intestine. As noted in the specification at page 5, patients suffering from Barrett's esophagus usually experience more serious than average gastroesophageal reflux.

By way of further support, Applicants attach herewith a reference, Fitzgerald, *Aliment. Pharmacol. Ther*, 2001, 15:269-276. Fitzgerald relates to Barrett's oesophagus, as a complication resulting from gastroesophageal refulux disease (GERD) and an important risk factor for adnocarcinoma.

As indicated by Fitzgerald (at pages 272-273), symptoms have been relieved in only some cases with the treatment with omeprazole or lansoprazole. Even in some cases it is not certain that acid exposure has been completely suppressed by this treatment. For example, Fitzgerald states that, "regression of dysplasia has not been observed in clinical studies involving PPIs." (page 274 lines 1-2). This statement can also be anologized to the nocturak GERD, which relates to Barrett's oesophagus.

Applicants also submit herewith another reference, Sachs, *Aliment. Pharmacol. Ther*, 2006, 23 (Suppl. 2): 2-8. As mentioned in the summary of Sachs, all PPIs must undergo acid accumulation in the parietal cell through protonation, followed by a second protonation which results in the activation, *i.e.*, a mechanism of action comprising two steps, thus corresponding to two pKa values. The accumulation of PPI in the parietal cells relies on the first pKa of the pyridine ring, while the second pKa is related to the benzimidazole nucleus (in the case of omeprzole and lansoprazole) or the imidazopyridine nucleus (in the case of tenatoprazole). This second pKa affects the stability of the inhibition of gastric acid secretion (see page 4 right column). All PPIs bind to Cysteine 813 which is in the luminal vestibule of the pump and accesible to reducing agents that reverse the inhibition. Tenatoprazole additionally binds to Cysteine 822 which is located deep in the membrane.

As further explained by Sachs, this is consistent with the fact that omeprazole inhibition effect can be reversed, whereas the inhibitory effect of tenatoprazole is stable (which explains the difference in the 2nd pKa value as noted by Sachs in Table 1, page 4 left column). This is also consistent the Fitzgerald reference cited above, which sets forththe unsatisfactory results obtained with omeprazole and lansoprazole in the treatment of nocturnal reflux and Barrett's oesophagus.

In contract, the methods of the present invention allow for the effective treatment of nocturnal reflux and Barrett's oesophagus using tentoprazole. As set forth in the present specification at page 5, lines 7-16, tenatoprazole provides "a greater degree of relief from the atypical symptoms of gastroesophageal reflux, and more particularly nocturnal, ..." and also at page 5, lines 18-22): "...can also act effectively on Barrett's oesophagus, or endobrachyoesophagus, which is defined by the presence of an intestinal-type mucosa (cylindrical) at the level of the lower oesophagus or the gastroesophageal junction."

A comparison of some pharmacokinetic properties (*e.g.*, AUC values) of tenatoprazole with those of omeprazole and lansoprazole is mentioned page 7 lines 8-15 where it is stated that "tenatoprazole can counteract the proton pump regeneration phenomenon by maintaining an inhibitory concentration for a sufficiently long period of time to meet the two criteria specified previously". As mentioned in the following paragraph (at page 7) tenatoprazole is effective "to treat diseases for which the treatments currently available are of poor efficacy, in particular atypical and oesophageal symptoms of

gastroesophageal reflux, dyspepsia and Barrett's oesophagus". In support, the results of studies are mentioned in Table 2 and following.

Thus the description demonstrates that tenatophrazole can be effectively used in the treatment of nocturnal GERD and Barrett's oesophagus with unexpected results, as confirmed by Sachs, in contrast with omeprazole and lansoprazole, as mentioned by Fitzgerald.

Accordingly, Applicants submit that the requirements for enablement, as set forth in *Forman*, have been satisfied. As such, the skilled artisan would not require undue experimentation to practice the present methods. For at least the above reasons, Applicants request that the rejections under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection under 35 U.S.C. § 102(e)

Claims 1 and 11-21 are rejected under 35 U.S.C. § 102(e) as purportedly anticipated by Barth et al., U.S. Publication No. 2006/0024238 ("Barth"). Applicants submit that Barth fails to disclose each and every element of the presently claimed invention.

Barth discloses formulations for nasal administration, comprising PPIs, more particularly rabeprazole, for use in the treatment of GERD and various gastro-intestinal diseases. Barth does not disclose tenatoprazole for the specific treatment of nocturnal GERD and Barrett's oesophagus. Accordingly, Barth does not recite each and every element of the presently claimed invention. Applicants request that this rejection be withdrawn.

Conclusion

For the reasons noted above, the art of record does not disclose or suggest the present claims.

In view of the foregoing amendments and remarks, reconsideration of the claims and allowance of the subject application is earnestly solicited. The Examiner is invited to contact the undersigned at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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